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EXAMINER	
SOUAYA, JEHANNE E	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 12/04/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/773,307	EGASHIRA ET AL.	
	Examiner	Art Unit	
	Jehanne E Souaya	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1 and 2* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1 and 2* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *16* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's election of Group I, without traverse, in the paper filed August 28, 2002 is acknowledged. An action on the merits of Group I, claim 2, with regard to the abnormality at amino acid residue 140 of the CD38 gene, as well as claim 1, follows.

Priority

2. The declaration filed July 20, 2001, indicates a prior foreign application, Japanese application 2000-316578, however the declaration indicates that priority is not claimed, therefore the effective filing date of the instant application is the actual filing date of the application, January 31, 2001. If the declaration is in error, appropriate correction is required. Further, if such is the case, applicant should note that a certified copy of the foreign priority document is not present. See MPEP 201.14(b).

Specification

3. The disclosure is objected to because of the following: the drawings (Figs 6-12) contain amino acid and nucleic acid sequences that are not designated by SEQ ID NO either in the drawings themselves or in the "Brief Description of the Drawings" section in the specification. Furthermore, it appears that such sequences are not designated in the "Sequence Listing". A SEQ ID NO must designate each disclosure of an amino acid or nucleic acid sequence. However, fragments of sequences can be designated as follows: for example, "amino acids 3-8 of SEQ ID NO 1", instead of making the fragment it's own SEQ ID NO. It cannot be determined, however, what fragments the sequences in the drawings correspond to. Applicant is required to either amend the sequence listing to

designate the additional sequences in the drawings, or to designate which SEQ ID NO, or fragment of an already disclosed SEQ ID NO, in the sequence listing that they correspond to either in the "Brief Description of the Drawings" or the drawings themselves. Applicant is further reminded that if the drawings are to be amended, new drawings must be submitted. Appropriate correction is required.

Claim Rejections - 35 USC § 112

Enablement

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-2 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

6. There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue (See In re Wands, 858 F. 2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). These factors include, but are not limited to:

Quantity of Experimentation Necessary
Amount of Direction and Guidance
Presence and Absence of Working Examples
Nature of the Invention

Level of predictability and unpredictability in the art

The claims are broadly drawn to methods of detecting a risk factor for diabetic onset in an individual by detecting any genetic abnormality of the CD38 gene, including any abnormality of the CD38 gene at the site encoding arginine at amino acid 140. The specification, however, does not enable one of skill in the art to practice the invention as broadly as it is claimed.

Firstly, the claims are drawn to detecting any "risk factor", however the claims do no establish any association between an increased or decreased risk, for example, and presence of any abnormality or specific abnormalities in the CD38 gene. Further, the specification defines the term "risk factor", broadly. The specification teaches that a mutational analysis of the CD38 "gene" was carried out with DGGE using 240 subjects who had been diagnosed as diabetic (p. 19). The specification, however, does not teach what type of diabetes the subjects were suffering from (for example: type I or type II). With respect to such, the specification defines "risk factor" as a factor associated with 1) knowing what type of diabetes a diabetic individual suffers from; and/or 2) to predict whether or not an individual who presently appears healthy carries risk factors that are capable of causing diabetes in the future, therefore the claims encompass determining what type of diabetes an individual suffers from, however the specification has provided no evidence or comparison between type I or type II diabetic patients for the skilled artisan to be able to determine a predictable correlation between any genetic abnormality in the CD38 gene and what type of diabetes a patient is suffering from. It is known in the art, and the specification teaches that different types of diabetes exist. Further, the art teaches that mutations in certain genes, for example, are only associated with a specific

type of diabetes (see for example Kondo et al, Diabetes, vol. 51, July 2002, pp 2325-2328, which teaches that an adiponectin mutation is associated with Type II diabetes).

The claims further broadly encompass detecting any abnormality in the CD38 gene. With respect to the CD38 gene, neither the specification nor the art teach the complete nucleotide sequence of the CD38 gene, including 5' and 3' untranslated regions, promoter, intron and exons. Therefore, neither the specification nor the art enable the skilled artisan to determine any abnormality in sequences that have not been taught (that is, undisclosed sequences of the CD38 gene) or to correlate such with a risk for diabetes. With respect to the term "abnormality", such encompasses any mutation, such as substitutions, deletions, or additions of nucleic acids that lead to silent, missense, frameshift, or truncation mutations, that may or may not alter the function or expression of the CD38 protein. The specification, however, only teaches specific nucleic acid substitutions that lead to missense or silent mutations. Furthermore, the specification and the art teach that some of these mutations are not associated with diabetes. The specification teaches detecting 5 mutations, C348A (silent mutation at codon 116), C418T (missense at codon 140 of CD38 protein: Arginine to Tryptophan), A504C (silent at codon 168), C791T (missense at codon 264; Serine to leucine), and –28G/A in intron 7, however, while the specific substitution of a C to a T at nucleic acid position 418 which leads to a tryptophan residue at position 140 was found in 3.7 % of diabetic patients (again the specification does not teach what type of diabetes the patients suffered from) and 1.5 % of controls (p. 31), the art (Okamoto et al., Chemical Immunology, 2000, vol. 75, pp 121-145) teaches (the specification does not teach the results of control patients with respect to this mutation) that A504C substitution which leads to a silent

mutation at amino acid 168 was found in 16% of NIDDM patients as well as control subjects (p. 136). Further, it is unclear from the teachings in the specification, whether some of the mutations found are statistically associated with an increased risk for diabetes. For example, the specification teaches that the intron 7, -28G/A mutation was found in 1.2% of diabetic patients (it is again noted that the specification does not teach what type of diabetes the patients suffered from) and 1% of controls. There is no guidance in the specification, however, as to whether the .2% difference between diabetics and controls is statistically significant. Based on such teachings, the skilled artisan would not be able to establish a predictable correlation that *any* abnormality in the CD38 gene would indicate either what type of diabetes a patient was suffering from, or whether or not *any* abnormality indicated an increased or decreased risk of developing diabetes, without further undue experimentation.

Claim 2 is further drawn to detecting any abnormality at position 140 of the CD38 protein, however, as discussed above, the specification only teaches a single missense mutation at this site, the substitution of a tryptophan for an arginine residue at codon 140. While the specification teaches this mutation was found in 3.7% of diabetic patients (again, the specification does not discuss what type of diabetes the patients suffered from) and 1.5% of controls, the specification does not teach any other abnormalities, such as any other amino acid substitutions, deletions, insertions, frameshifts or truncations at this site, such that the skilled artisan would be able to establish a predictable correlation between any abnormality at this site and the type of diabetes a subject suffers from or whether the abnormality is associated with an increased or decreased risk for developing diabetes. It is noted that the specification teaches that the arginine to tryptophan mutation

at position 140 showed lower activity of both ADP ribosyl cyclase and cyclic ADP-ribose hydrolase, however the specification provides no guidance as to whether any mutation at this site will have the same affects (for example the substitution of an acidic residue such as glutamic acid, or a non polar residue such as valine) or whether the lower activity of both ADP ribosyl cyclase and cyclic ADP-ribose hydrolase are in fact responsible for the diabetic onset of the patients in which the mutation was found.

Therefore, based on the lack of guidance from the specification as outlined above and the unpredictability taught in the art with respect to mutations in CD38 which are not associated with diabetes, the skilled artisan would have to perform undue experimentation. To practice the invention as broadly as it is claimed, the skilled artisan would have to establish whether a certain type of mutation in the CD38 gene was associated with a specific type of diabetes (for example, truncation mutations vs. missense mutations), or whether mutations in specific regions, (ie: hotspots) were associated with a specific type of diabetes. To be able to find a correlation between types of mutations and the type of diabetes they are found in, the skilled artisan would have to perform a large study to screen patients with a specific type of diabetes and control patients for any number of mutations in different regions of the CD38 gene to establish whether any abnormality in the gene is associated with diabetic onset. This experimentation is considered undue because each step requires trial and error analysis, the results of which are unpredictable, as exemplified by the teachings in the specification and the art, which demonstrate that only two of the 5 CD38 mutations taught by the specification are found in a larger number of diabetic patients vs controls (it is noted that based on the lack of statistical discussion with regard to the intron 7, -28G/A mutation,

the skilled artisan would not be able to determine whether the .2% difference in incidence of the mutation between diabetics and controls was statistically significant). Given the large number of possible abnormalities that could be found in the CD38 gene, the teaching of 2 missense mutations in different regions of the CD38 protein which were found in a larger number of diabetics vs controls (R140W: 3.7% to 1.5% and S264L: 1.2% vs 0), and the teaching of 3 mutations (2 silent and 1 substitution in an intron) of which the art teaches that 1 is not statistically associated (A504C) and the specification provides no guidance as to whether the remaining two are statistically associated, the skilled artisan would not be able to establish a predictable correlation between the presence of any abnormality in the CD38 gene and a specific type of diabetes or an increased risk for developing diabetes, without undue experimentation.

Written Description

7. Claims 1-2 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to methods of detecting a risk factor for diabetic onset in an individual by detecting any genetic abnormality of the CD38 gene, including any abnormality of the CD38 gene at the site encoding arginine at amino acid 140. With respect to the CD38 gene, neither the specification nor the art teach the complete nucleotide sequence of the CD38 gene, including 5' and 3' untranslated regions, promoter, intron and exons. With respect to the term "abnormality", such encompasses

any mutation, such as substitutions, deletions, or additions of nucleic acids that lead to silent, missense, frameshift, or truncation mutations, that may or may not alter the function or expression of the CD38 protein. The specification, however, only teaches two missense mutations and 3 silent mutations. Given the large number of possible abnormalities that could be found in the CD38 gene, the teaching of 2 missense mutations in different regions of the CD38 protein which appear to be correlated in diabetic patients vs controls does not represent a "substantial portion" of the claimed genus of substitutions, deletions, or additions of nucleic acids that lead to silent, missense, frameshift, or truncation mutations, that may or may not alter the function or expression of the CD38 protein that are encompassed by the broadly claimed invention. Further, with respect to the recitation of "risk factor", the specification defines such as a factor associated with 1) knowing what type of diabetes a diabetic individual suffers from; and/or 2) to predict whether or not an individual who presently appears healthy carries risk factors that are capable of causing diabetes in the future. The specification, however, does not teach what type of diabetes the subjects were suffering from (for example: type I or type II).

Claim 2 is further drawn to detecting any abnormality at position 140 of the CD38 protein, however, as discussed above, the specification only teaches a single missense mutation at this site, the substitution of a tryptophan for an arginine residue at codon 140. While the specification teaches this mutation was found in 3.7% of diabetic patients (again, the specification does not discuss what type of diabetes the patients suffered from) and 1.5% of controls, the specification does not teach any other abnormalities, such as any other amino acid substitutions, deletions, insertions, frameshifts or truncations at this

site, such that the skilled artisan would be able to establish a predictable correlation between any abnormality at this site and the type of diabetes a subject suffers from or whether the abnormality is associated with an increased or decreased risk for developing diabetes. It is noted that the specification teaches that the arginine to tryptophan mutation at position 140 showed lower activity of both ADP ribosyl cyclase and cyclic ADP-ribose hydrolase, however the specification provides no guidance as to whether any mutation at this site will have the same affects (for example the substitution of an acidic residue such as glutamic acid, or a non polar residue such as valine) or whether the lower activity of both ADP ribosyl cyclase and cyclic ADP-ribose hydrolase are in fact responsible for the diabetic onset of the patients in which the mutation was found.

The specification provides insufficient written description to support the genus encompassed by the claims.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993), and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of

written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966.
>
> An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

Accordingly, the specification does not provide a written description of the invention of claims 1 and 2.

Indefinite

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-2 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite because the claim fails to include a positive process step relating back to the preamble. The preamble states a method for detecting a risk factor for diabetic onset but the final process step is detecting an abnormality in the CD38 gene.

Therefore the method is unclear as to whether it is to detecting a risk factor or to detecting an abnormality in a gene.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 1-2 are rejected under 35 U.S.C. 102(b) as being anticipated by Kazuo et al. (Bunshi Tonyobyogaku, 1998, vol. 9, English abstract).

Kazuo et al teach that the allele frequency of a missense mutation of R140W of the CD38 gene was different between patients with NIDDM and nondiabetic controls. Kasuo et al teach that this mutation indicated the involvement of the CD38 gene in the pathogenesis of NIDDM. Therefore, Kasuo et al inherently teach a method of detecting a risk factor for diabetic onset by detecting a missense mutation at position 140 of the CD38 protein.

12. Claims 1-2 are rejected under 35 U.S.C. 102(b) as being anticipated by Yagui et al (Diabetologia, vol. 41, pp 1024-1028, 1998).

Yagui et al teach detecting a mutation in the exon 3 of CD38 that corresponds to a missense mutation in the CD38 protein of an Arg to Trp, appears to contribute to the development of Type II diabetes mellitus (see abstract, Fig 2, p. 1026, col 1-2).

Therefore, Yagui et al inherently teach a method of detecting a risk factor for diabetic onset by detecting a missense mutation at position 140 of the CD38 protein.

Conclusion

13. No claims are allowable over the cited prior art.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jehanne Souaya whose telephone number is (703) 308-6565. The examiner can normally be reached Monday-Friday from 9:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 305-3014. Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jehanne Souaya
Patent examiner
Art Unit 1634

Jehanne Souaya
11/25/2002